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(54) Title: STABLE AQUEOUS FOLINATE SOLUTION

(57) Abstract

The invention provides an aqueous folinate solution suitable for medical applications in the form of a sodium folinate solution which is stable when stored at refrigerator temperatures, i.e. does not crystallize.

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Stable aqueous folinate solution.

The invention relates to a stable aqueous folinate solution.

Folinic acid is a metabolite of folic acid and is the active form into which folic acid is converted in the body. This conversion is inhibited by some cytostatics such as methotrexate. In order to overcome this problem, folinic acid has to be added. Folinic acid is further used in the case of folic acid deficiency, and it has a synergistic effect in combination with 5-fluorouracil. The customary form in which folinic acid is added is calcium folinate which is administered by infusion or injection. Calcium folinate is readily soluble but it does not keep at room temperature and can therefore not be stored for prolonged periods at room temperature. At refrigerator temperatures, where the folinate does store well, a relatively concentrated solution is not stable; at the normal refrigerator temperature of approximately 4°C, crystallization takes place at a concentration of as little as 15 mg/ml.

EP 0 401 895 provides folinate solutions with a relatively high concentration which are stable at refrigerator temperature. These solutions contain folinate ions, calcium ions and a complexing agent for calcium. The complexing agent and calcium form a complex. These solutions may be stable at refrigerator temperature in a concentration of as much as 50 mg/ml of folinate. The complexing agent used can be, for example, a sodium salt of ethylenediaminetetraacetic acid.

It has been found that a stable aqueous solution of folinic acid can be obtained simply by preparing an aqueous solution of sodium folinate solution. Even in a high concentration, up to about 400 mg of folinic acid per ml, it is stable in the refrigerator, i.e. does not crystallize. The solution is stable at a pH range of 4.0 to 10.0; especially from 6.0 to 10.0; preferable about 8.0 to 9.0.

Preferably, the solution contains a stabilizer,

such as sodium citrate or sodium acetate. These salts further increase the stability of the solution. The present folinate solution also comprises an isotonizing agent such as sodium chloride.

It is also advantageous to incorporate a pharmacheutically acceptable buffer into the aqueous folinate solution according to the invention. Said buffer is preferably tris, a phosphate or a carbonate buffer, and is present in a concentration which is effective for obtaining the required pH.

The invention is further explained in the following examples.

Example 1

The following injection fluid was prepared:

Folinic acid (as sodium folinate)	25 mg
Sodium chloride	4.3 mg
Sodium citrate	0.5 mg
Water for injection to make up to	1 ml

The pH had been set to a value of 7.5 by means of sodium hydroxide. The purpose of the sodium chloride was to make the solution isotonic.

The abovementioned solution was found still to be stable after 3 months at refrigerator temperature between 2 and 8°C (on average approximately 4°C), i.e. it had not crystallized out.

Example 2

The following injection fluid was prepared:

Folinic acid (as its sodium salt)	25.0 mg
Sodium citrate	0.50 mg
Sodium chloride	4.00 mg
Tris	1.21 mg
Sodium hydroxide / hydrogen chloride	q.s.(pH 8.0)
Water for injection to make up to	1 ml

The thus obtained injeciton fluid was still stable after 3 months at refrigerator temperature.

Example 3

An injection fluid was prepared, having the following components:

Folinic acid (as its sodium salt)	25.0 mg

Sodium citrate	0.25 mg
Sodium chloride	4.00 mg
Tris	1.21 mg
Sodium hydroxide / hydrogen chloride	q.s.(pH 9.0)
Water for injection to make up to	1 ml

The obtained injection fluid was still stable after 3 months at refrigerator temperature.

Example 4

An injection fluid was prepared, having the following components:

Folinic acid (as its sodium salt)	25.0 mg
Sodium citrate	0.50 mg
Sodium chloride	4.00 mg
Sodium hydroxide / hydrogen chloride	q.s.(pH 7.5)
Water for injection to make up to	1 ml

This injection preparation was still stable after 3 months at refrigerator temperature.

Example 5

An injection fluid was prepared, having the following components:

Folinic acid (as its sodium salt)	25.0 mg
Sodium citrate	0.25 mg
Sodium acetate	0.25 mg
Sodium chloride	4.00 mg
$Na\ H_2\ PO_4\ .\ 1\ H_2O$	0.134 mg
$Na_2\ H\ PO_4\ .\ 2\ H_2O$	1.61 mg
Sodium hydroxide / hydrogen chloride	q.s.(pH 8.0)
Water for injection to make up to	1 ml

This preparation was still stable after 3 months at refrigerator temperature.

Example 6

An injection fluid was prepared, having the following components:

Folinic acid (as its sodium salt)	25.0 mg
Glucose	25.0 mg
Sodium citrate	0.50 mg
Tris	1.21 mg
Sodium hydroxide / hydrogen chloride	q.s.(pH 8.0)
Water for injection to make up to	1 ml

This injection preparation was still stable after 3 months at refrigerator temperature.

CLAIMS

1. Aqueous folinate solution for pharmaceutical applications, characterized in that said solution contains the folinate in the form of sodium folinate, in a concentration of up to about 400 mg of folinic acid per ml, said solution having a pH in the range of approximately 4.0 to 10.0.

2. Aqueous folinate solution according to claim 1, characterized in that the pH of the solution is from about 8.0 to about 9.0.

3. Aqueous folinate solution according to claim 1 or 2, characterized in that said solution also comprises a stabilizer.

4. Aqueous folinate solution according to claim 3, characterized in that said stabilizer is selected from sodium citrate or sodium acetate.

5. Aqueous folinate solution according to one or more of the claims 1 to 4, characterized in that said solution also comprises an isotonizing agent.

6. Aqueous folinate solution according to claim 5, characterized in that said isotonizing agent is sodium chloride.

7. Aqueous folinate solution according to one or more of the claims 1 to 6, characterized in that said solution also comprises a pharmaceutically acceptable buffer, selected from the group consisting of tris, phosphate, and carbonate buffer materials.

INTERNATIONAL SEARCH REPORT

Intern. al Application No
PCT/NL 95/00126

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D475/04 A61K31/525

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US,A,2 695 860 (JOSEPH FRANCIS WEIDENHEIMER ET AL) 30 November 1954 *Complete document: particularly claim 2* ---	1
A	EP,A,0 401 895 (PHARMACHEMIE B.V.) 12 December 1990 cited in the application *Complete document* -----	1

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Name and mailing address of the ISA	Authorized officer
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INTERNATIONAL SEARCH REPORT

information on patent family members

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EP-A-0401895	12-12-90	NL-A-	8901432	02-01-91
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